

Strategies for Primary Prevention of Atopy in Children

Christina E. Ciaccio, MD, and Jay M. Portnoy, MD

Corresponding author

Jay M. Portnoy, MD
Section of Allergy, Asthma, and Immunology,
Children's Mercy Hospitals and Clinics, 2401 Gillham Road,
Kansas City, MO 64108, USA.
E-mail: jportnoy@cmh.edu

Current Allergy and Asthma Reports 2008, 8:493–499
Current Medicine Group LLC ISSN 1529-7322
Copyright © 2008 by Current Medicine Group LLC

In recent decades, the prevalence of atopic diseases such as asthma, hayfever, food allergy, and atopic dermatitis has been steadily increasing. Unfortunately, more advances have been made in secondary prevention of symptoms and exacerbations than in primary prevention. One barrier to adopting prevention strategies is uncertainty regarding the cause of atopy. A genetic predisposition has been well documented. However, other factors, including diet, environment, infections, medications, and gastrointestinal flora, all play a role in the development of atopic disease. Modifying these factors holds promise for stopping the atopic march in the future. This paper reviews advances that have been made in the primary prevention of atopic disease.

Introduction

In recent decades, the prevalence of atopic diseases such as asthma, allergic rhinitis, food allergy, and atopic dermatitis has been steadily increasing. The incidence of asthma has increased 160% among children up to age 4 years, and at least \$1.2 billion is spent each year on treating allergic rhinitis alone [1]. The incidence of peanut allergy has doubled in the past decade, whereas atopic dermatitis accounted for approximately 7.4 million outpatient and emergency department visits for children over a recent 8-year period [2,3]. These staggering statistics demonstrate the importance of developing effective strategies to reduce the morbidity and mortality associated with these diseases. Although huge advances have been made in developing treatments that are effective in preventing symptoms and reducing morbidity, the more desirable goal of primary prevention of atopy has remained elusive.

Part of the difficulty in finding effective preventive strategies is the lack of consensus on the underlying cause

of atopic diseases. Although a genetic predisposition to atopy development has been well documented, other factors clearly are involved [4]. For example, after the reunification of East and West Germany, the incidence of allergic disease significantly increased in East Germany after the introduction of a “Western lifestyle,” strengthening the argument that environmental factors, especially during childhood, also play an important role in atopic disease development [5]. Diet, infections, allergen exposure, medications, and even household cleaners all have been implicated as contributing factors for atopic disease development. Although the precise causes of atopy remain unclear, several preventive strategies have been hypothesized and tested in recent years, leading to at least some success in preventing asthma, hayfever, food allergy, and atopic dermatitis (Table 1).

Preventive Strategies

Dietary strategies

One of the better researched preventive strategies is the manipulation of children's diets at various times of life. One widely held belief is that very young children have immature gastrointestinal tracts that do not tolerate highly antigenic foods [4]. For example, given the observed association between diet and development of atopic dermatitis [6,7], it has been hypothesized that if exposure to highly antigenic foods is delayed, the incidence of atopic dermatitis and the eventual development of other atopic diseases will decrease. Unfortunately, studies that eliminate antigenic foods have failed to definitively prove this to be an effective preventative strategy.

In 2006, a Cochrane review of four clinical trials with 314 participants concluded that maternal dietary antigen avoidance during pregnancy, including cow's milk and eggs, did not affect atopic dermatitis incidence in the first 18 months of life [8]. The review also cited one trial with 26 participants that concluded that maternal dietary antigen avoidance during breastfeeding did not affect the incidence of atopic dermatitis in the first 18 months of life. It concluded that an antigen-avoidance diet during pregnancy was unlikely to reduce a child's risk of atopy, although the effect of an antigen-avoidance diet during lactation was unclear. In 2008, Greer et al. [9••] published

Table 1. Referenced studies and their outcomes

Study	n	Intervention or observation	Outcome
Kramer and Kakuma [8]	314	Maternal dietary antigen avoidance during pregnancy	No protective effect against atopic disease
Zutavern et al. [10]	2000	Solid food introduction delayed	No protective effect against atopic disease
Chatzi et al. [11]	460	Mediterranean diet during pregnancy	Protected against wheeze and atopy at age 6 y
Willers et al. [12]	1924	Maternal diet monitored during pregnancy	Apples and fish protected against wheeze and atopy
Garcia-Marcos et al. [13•]	20,000	Mediterranean diet in children	Protected against chronic severe asthma in girls and against rhinitis
Chatzi et al. [14]	690	Mediterranean diet in children	Protected against wheezing and rhinitis
Weitzman et al. [15]	4331	Maternal tobacco use	Increased rate of asthma
Young et al. [16]	63	Parental tobacco use	Increased airway responsiveness
Martinez et al. [17]	700	Maternal tobacco use of > 10 cigarettes/d	Increased rate of asthma
Lannero et al. (BAMSE) [19••]	4089	Parental tobacco use after birth	Increased risk of IgE sensitization
Horak et al. (SPACE) [24]	700	Dust mite covers and education	No protective effect against symptomatic allergy
Custovic et al. [26]	620	Dust mite covers, HEPA vacuums, antimite foam	Protected against severe wheeze
Arshad et al. (Isle of Wight) [27•]	120	Common food allergen elimination, dust mite covers, antimite spray	Decreased sensitization to allergens up to age 8 y
Braun-Fahrlander et al. (ALEX) [31]	2618	Measured endotoxin level in mattress	Inverse relationship with asthma and rhinitis
Schram-Bijkerk et al. (PARSIFAL) [33]	6630	Measured endotoxin level in mattress	No relationship with asthma or rhinitis
Lehtinen et al. [34•]	118	Prednisolone given with viral infection	Decreased incidence of recurrent wheeze at 1 y
Davey et al. [37]	7649	Acetaminophen use	Increased rhinitis and wheeze
Kozyrskyj et al. [39]	13,000	Antibiotic use in rural infants	Increased risk of asthma
Celedon et al. [40]	448	Antibiotic use in urban infants	No increase in asthma
Kukkonen et al. [41]	1223	High-risk infants and mothers given probiotics	Protected against atopic dermatitis
Lee et al. [42]	1581	Meta-analysis of probiotic use	May protect against atopic dermatitis

ALEX—Allergy and Endotoxin study; BAMSE—Stockholm Children Allergy and Environmental Prospective Birth Cohort; HEPA—high-efficiency particulate air; PARSIFAL—Prevention of Allergy–Risk Factors for Sensitization Related to Farming and Anthroposophic Lifestyle study; SPACE—Study of Prevention of Allergy in Children in Europe.

a consensus statement on behalf of the American Academy of Pediatrics on the effects of early nutritional interventions on atopic disease development. Although the authors also mostly discouraged delaying exposure to antigenic foods, citing insufficient data to support the prevention of atopic disease, the group did conclude that for infants at high risk of developing atopy, breastfeeding exclusively for at least 4 months with supplements of hydrolyzed infant formulas may decrease the risk of atopic dermatitis compared with breastfeeding and supplementation with cow milk–based formula. This is less likely to apply to infants at low risk of developing atopy, however, and exclusive breastfeeding beyond 3 to 4 months does not give additional benefit

in preventing atopic dermatitis. Furthermore, the group stated that whereas breastfeeding seems to decrease the number of wheezing episodes in children less than 4 years old, exclusive breastfeeding cannot be said to protect high-risk infants from asthma after age 6 years. The role of breastfeeding in preventing or delaying food allergies cannot be determined at this time.

In regard to the effect of timing of the introduction of complementary foods on atopic disease, Greer et al. [9••] stated that the available data are conflicting and inconclusive. After the consensus report, Zutavern et al. [10] published data from a prospective birth cohort study of more than 2000 children that found no protective effect

of a delayed introduction of solids past 4 or 6 months on asthma, food allergy, or allergic rhinitis at age 6 years. This group did find that avoiding solid food for the first 4 to 6 months was associated with increased food sensitization. Even though antigen-avoidance strategies have been disappointing thus far, diet and nutrition almost certainly play a role in atopic disease development.

The reduced intake of antioxidant vitamins (β -carotene and vitamins A, C, and E) and mineral cofactors essential for antioxidant defense mechanisms (selenium, zinc, and copper) as a result of reduced consumption of meat, fresh fish, fruit, and vegetables in Western diets has been implicated as a cause of the increased prevalence of asthma. Chatzi et al. [11] evaluated the impact of maternal adherence to a Mediterranean diet on asthma and atopy development in childhood. A total of 460 mothers and children were observed for 6 years. A high Mediterranean diet score during pregnancy was found to be protective against persistent wheeze, atopic wheeze, and atopy at age 6 years [11]. In a second study, Willers et al. [12] failed to find a protective effect of the consumption of most foods on development of atopy; however, they did find a significant protective effect of apples and fish on the development of childhood asthma and allergic disease.

The potential protective effect of a healthful diet also has been seen in studies examining children's diets. One study conducted with more than 20,000 6- and 7-year-old Spanish children also found a significant preventive effect when children's diets were high in fruits, vegetables, legumes, fish, and whole grain. This study found that each Mediterranean score unit had a small but protective effect on chronic severe asthma in girls [13•]. Specifically, more frequent intake of seafood and cereals protected against chronic severe asthma, whereas consumption of fast food was a risk factor for it. In addition, seafood and fruit consumption were protective against rhinoconjunctivitis. Chatzi et al. [14] found similar protective effects from the consumption of oily fish. This group surveyed 690 children ages 7 to 18 years living in rural Crete and found a beneficial effect of commonly consumed fruits, vegetables, and nuts on symptoms of asthma and rhinitis. The intake of grapes, oranges, apples, and fresh tomatoes was protective against wheezing and rhinitis [14]. Furthermore, high consumption of nuts was inversely associated with wheezing, whereas margarine consumption increased the risk of wheezing and allergic rhinitis. This evidence suggests that more emphasis should be placed on encouraging a healthful maternal and childhood diet that is high in fruits, vegetables, legumes, oily fish, and whole grains and low in trans fat and simple sugars as a preventive strategy. More evidence is needed to support the widely held belief that food antigen avoidance decreases the likelihood of atopy development.

Environmental control

Another concern among researchers and clinicians is the ever-changing milieu of allergens, chemicals, and tox-

ins in the environment. From a prevention perspective, determining which exposures from our vast environment increase the incidence of atopic disease has proven to be quite difficult. One of the best-studied pollutants in the context of atopic disease development is environmental tobacco smoke (ETS). ETS has long been implicated in asthma development and recently has also been implicated in the development of IgE sensitization to indoor allergens and food allergens [15–17]. Although some will argue that children exposed to ETS also tend to have a decreased antioxidant intake and a more sedentary lifestyle, many compelling studies implicate ETS as a cause of asthma and other atopic diseases.

In 1990, Weitzman et al. [15] analyzed data from the Child Health Supplement to the 1981 National Health Interview Survey that included 4331 children up to 5 years old. They concluded that maternal smoking is associated with higher rates of asthma, an increased likelihood of using asthma medications, and an earlier disease onset [15]. In 1991, Young et al. [16] published a study of 63 infants that showed elevated levels of airway responsiveness at an early age in children of smoking parents. In 1992, children of mothers who smoked 10 or more cigarettes per day were found to be 2.5 times more likely to develop asthma than children of mothers who did not smoke or who smoked fewer than 10 cigarettes per day [17].

An ongoing study, the Stockholm Children Allergy and Environmental Prospective Birth Cohort (BAMSE), is observing a birth cohort of 4089 infants for 2 years by parental questionnaire. This study initially found an increase in recurrent wheezing when the mother smoked during pregnancy. These data were again examined recently for evidence of an increased risk of IgE sensitization after ETS exposure. A 1998 meta-analysis found that parental smoking before or immediately after birth is unlikely to increase the risk of allergic sensitization in children [18]. The BAMSE data agreed that no apparent association exists between maternal smoking during pregnancy and the risk of IgE sensitization. However, in contrast to the previous meta-analysis, a dose-response relationship was found between exposure to ETS from parental smoking during the first few months of life and IgE sensitization [19••]. These data strongly support aggressive counseling toward smoking cessation for all parents and expecting mothers.

Another common environmental exposure, house dust mites, also has been implicated in asthma development [20,21]. Children exposed to high levels of dust mites in their first 3 years of life are more likely to be sensitized to dust mites between ages 3 and 7 years [22,23]. As such, an attempt has been made to prevent asthma via simple house dust mite avoidance measures. The Study of Prevention of Allergy in Children in Europe (SPACE) recruited almost 700 children from birth until 2 years of age who were at high risk of sensitization to dust mites. The intervention group was given dust mite covers and education

on allergen avoidance. The group found that dust mite avoidance did not show a protective effect on the development of sensitization to dust mite or symptomatic allergy in children [24].

The Manchester Asthma and Allergy Study used more aggressive avoidance measures in an attempt to prevent sensitization to dust mites, including dust mite covers on the mother's bed from the second trimester of pregnancy, dust mite covers for the child's bed, hardwood flooring in the bedrooms, high-efficiency particulate air vacuum cleaners, and application of the antimite foam benzyl benzoate on soft furniture. Although exposure to dust mite, cat, and dog allergens was significantly reduced [25], no difference in mite sensitization, mild wheeze, cough, or atopic dermatitis at 1 year of age was found. However, a significant difference was seen in the incidence of severe wheeze in the intervention group [26].

One large trial published in 2007 combined food and dust mite avoidance to attempt to prevent atopic sensitization in high-risk children. The Isle of Wight prevention study randomized 120 children at high risk for atopic disease into an intervention group and a control group. The intervention included strict elimination of common food allergens, including cow's milk products, eggs, wheat, nuts, fish, and soy, until age 12 months. Lactating mothers followed the same restricted diet but were allowed to consume wheat products. Extensively hydrolyzed formula was given for supplementation to the child from birth or when breastfeeding was discontinued before 9 months. Dust mite avoidance was achieved by treating the carpets and upholstery in the infant's bedroom with an antimite spray—acaricide—and dust mite covers were placed on the child's mattress. Again, dust mite allergen was significantly reduced in the intervention group. These data did reveal a significant reduction in sensitization to allergens, including dust mites, up to 8 years of age. The intervention group also showed a reduced prevalence of asthma and atopic dermatitis at 1 year and asthma at 8 years of age [27•]. This trial was the first to find that strict food and dust mite avoidance in a select group of high-risk infants may be an effective preventive strategy against the development of allergic sensitization.

Microbial exposure

The assumption that strict avoidance of all known allergens in all groups of children will prevent atopy cannot be made, however. Large amounts of data suggest that living on a farm, an environment filled with allergens, is also protective against atopy development. Since 1999, at least 15 studies conducted in rural Europe have shown a decreased prevalence of allergic rhinoconjunctivitis [28]. Several of these studies also confirmed a decrease in IgE sensitization by skin prick or specific IgE testing. Furthermore, this protective effect seems to last into adulthood even if one does not continue to live on a farm. However, moving to a farm in adulthood does not offer similar

protective effects, and starting farm animal contact in adulthood actually increases one's risk of developing atopic sensitization.

Unfortunately, a preventive strategy cannot be developed based on these observations because the exact protective mechanism of living in a farming environment remains a mystery. In 1989, Strachan [29] proposed the hygiene hypothesis to explain the similar observation that children in larger families were less likely to develop hayfever and eczema. The hypothesis states that a lack of early childhood exposure to infectious agents increases susceptibility to allergic diseases by modulating immune system development. This hypothesis' major proposed mechanism is that the developing immune system requires repeated stimuli from bacteria and parasites to develop regulatory T cells that suppress T-helper type 1 and type 2 (Th1 and Th2) responses that would otherwise lead to autoimmune and atopic disease, respectively.

Endotoxin, from gram-negative bacteria, and muramic acid, a component of peptidoglycan from the cell wall of all types of bacteria, have been found to be more abundant in mattress dust from farm children's beds [30]. Extracellular polysaccharide from *Penicillium* and *Aspergillus* spp (common indoor molds) is also more prevalent in farming households. According to the hygiene hypothesis, these observations would explain the farming environment's protective effect.

Two large European trials attempted to determine whether exposure to these microbial components was protective against atopy development. The Allergy and Endotoxin study, comprised of 2618 school-aged children in Austria, Germany, and Switzerland, found an inverse relationship between the level of endotoxin in children's mattresses and the development of atopic asthma and allergic rhinitis [31]. In addition, the level of muramic acid in mattresses was found to be inversely associated with wheeze independent of endotoxin levels [32]. However, the larger PARSIFAL (Prevention of Allergy—Risk Factors for Sensitization Related to Farming and Anthroposophic Lifestyle) study, made up of 6630 children in five European countries, found no association between endotoxin and atopy development after adjusting for the levels of extracellular polysaccharide and glucans in the environment [33]. PARSIFAL further concluded that neither endotoxin nor extracellular polysaccharide could explain the relative protective effects of farm living. The authors proposed in their article's conclusion that another yet unknown component of fungal spores may protect against allergic disease. Although recommending against basic hygiene practices to prevent atopic sensitization is impractical, at least somewhat limiting measures aimed at avoiding bacteria and fungi may be reasonable.

Despite the potential benefits of exposure to some microbes as proposed by the hygiene hypothesis, some microbial exposures are known to cause asthma. Several recent studies have examined the relationship between

viral infections and asthma development. Most infant wheezing is related to viral infections [34•]. Respiratory syncytial virus (RSV) in particular leads to childhood asthma in as many as one third of RSV cases. Rhinovirus has only recently emerged as another important causative agent for asthma. Lehtinen et al. [34•] found that 50% of diagnosed cases of rhinovirus resulted in recurrent wheeze 1 year after infection. After making this observation, the group further hypothesized that suppressing the immune system during the time of infection may prevent the immune dysregulation started by the infection. They observed that giving prednisolone for first-time wheeze associated with rhinovirus significantly reduced the incidence of recurrent wheeze after 1 year. Prednisolone's preventive was also seen in the same cohort of children who had eczema regardless of a diagnosis of rhinovirus or RSV. The authors recommended that a similar prospective trial be designed to see if the results could be repeated. This observation does propose one possible preventive strategy for asthma triggered by viral infections in the future.

Exposure to medications

Other exposures in our environment have raised concern among researchers as possible causes of an increase in atopic disease. Several studies recently have linked some medication use to atopy development. In particular, acetaminophen, an analgesic widely used by children and pregnant women, has been implicated in atopic disease development [35]. The level of glutathione, an endogenous antioxidant, was reduced in lung tissue after high doses of acetaminophen were administered to animals [36]. Therefore, some hypothesize that the reduced levels of glutathione after acetaminophen consumption lead to atopic disease. In 2005, Davey et al. [37] surveyed 7649 adults and children from Butajira, Ethiopia, for symptoms of allergic disease, sensitization to dust mites and cockroaches, and acetaminophen use. This group found that allergic symptoms increased with frequency of acetaminophen use. Wheeze, nocturnal shortness of breath, rhinitis, eczema, and cockroach sensitization were more common among acetaminophen users [37].

This year, Perzanowski et al. [38] presented data from the Columbia Center for Children's Environmental Health birth cohort study of mothers of Dominican and African American children living in New York City. These data suggested that third trimester acetaminophen use increased the risk for wheeze at age 5 years in a population already at risk for developing asthma [38]. With the growing evidence that acetaminophen plays a role in atopic disease development, a large, randomized, controlled trial is needed to determine whether avoidance by pregnant mothers and young children would successfully decrease atopic disease development.

Another group of commonly used medications in Westernized countries that has been implicated in atopy

development is antibiotics. Researchers have surmised that the commensal microflora in our gastrointestinal tracts is more important to serving a protective role against atopic disease than microbes in our external environment. As such, some argue that antibiotics will alter the body's internal flora and thus predispose one to allergic disease development.

A group from Manitoba collected data from more than 13,000 children born in that Canadian province in 1995. Controlled for reverse causation, health care use bias, and well-known asthma risk factors, children receiving more than four courses of antibiotics in their first year of life were at 1.5 times the risk of having asthma at 7 years of age [39]. This is contrast to the results of a similar study by Celedon et al. [40], who failed to find a causal relationship [40]. The authors of the Manitoba study speculate that the difference lies in the population studied. Fifty percent of the children in the Manitoba cohort lived in rural areas, whereas the study by Celedon et al. [40] was comprised of children living in an urban setting. The gastrointestinal microflora in children in rural areas has higher levels of lactobacilli and bifidobacteria and lower levels of *Clostridium difficile*, the same colonization pattern found in nonatopic children [39]. Conversely, children living in urban areas have lower levels of lactobacilli and bifidobacteria and higher levels of *C. difficile* in their gastrointestinal tracts. Thus, antibiotics, particularly broad-spectrum cephalosporins, may significantly alter the gut flora of children living in rural areas while having little effect on the gut flora of children living in urban settings.

Use of probiotics

These data also suggest that supplementation with probiotics may positively impact the gastrointestinal tracts of children, thus preventing the development of atopic disease, an idea that also has been examined in recent years by European and American researchers. Kukkonen et al. [41] found that supplementing expectant mothers' diets and their newborn infants' diets with probiotics (including lactobacilli and bifidobacteria) did not reduce the overall incidence of atopic disease by age 2 years. However, the group did find that the incidence of atopic dermatitis—in particular IgE-associated atopic dermatitis—was significantly reduced compared with placebo [41]. Since then, other studies examining the relationship between probiotics and the development of atopic dermatitis have found conflicting results. However, Lee et al. [42] published a meta-analysis earlier this year compiling all similar data available. The group found 21 trials published between February 1997 and May 2007 and pooled the data from six prevention trials, including the data from Kukkonen et al. [41], resulting in 1581 cases. Lee et al. [42] also concluded from the compiled data that probiotics may be efficacious in the primary prevention of atopic dermatitis.

Conclusions

As no clear consensus on the causes and mechanisms of atopic sensitization exist, developing a consensus on reasonable measures to prevent atopy is nearly impossible. Although recent changes to diet, nutrition, toxin exposures, and allergen exposure all likely play a part in the increased incidence of atopic diseases, determining the exact milieu responsible has remained a mystery.

Although food antigen avoidance by itself has had disappointing results in preventing atopic disease, evidence does suggest that a healthful maternal and childhood diet high in fruits, vegetables, legumes, oily fish, and whole grains and low in trans fat and simple sugars may have a protective effect against atopic disease. Alternatively, a combined food antigen and dust mite avoidance protocol may be beneficial for a select high-risk group of children to avoid allergic sensitization and development of disease.

Considerable evidence also exists implicating ETS as a cause of asthma and possibly atopic sensitization. Therefore, smoking cessation should be advised to pregnant women and all parents of young children. Not so clear are the data regarding exposure to microbial agents. At least somewhat limiting measures aimed at avoiding bacteria and fungi may be reasonable. However, viral infections have a clear association with childhood asthma. Treating wheezing caused by documented rhinovirus infections in children with prednisolone may be beneficial in avoiding asthma, particularly in children with atopic dermatitis. Finally, evidence exists to indicate that some medications alter one's risk of developing atopy. Maternal and childhood avoidance of antibiotics and acetaminophen, if possible, and supplementation with probiotics also may reduce the risk of developing atopic disease.

Disclosures

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. Eichenfield LF, Hanifin JM, Beck LA, et al.: Atopic dermatitis and asthma: parallels in the evolution of treatment. *Pediatrics* 2003, 111:608–616.
 2. Sicherer SH, Munoz-Furlong A, Sampson HA: Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003, 112:1203–1207.
 3. Horii KA, Simon SD, Liu DY, Sharma V: Atopic dermatitis in children in the United States, 1997–2004: visit trends, patient and provider characteristics, and prescribing patterns. *Pediatrics* 2007, 120:e527–e534.
 4. Adkinson NF, Middleton E: *Middleton's Allergy: Principles & Practice*, edn 6. St. Louis, MO: Mosby; 2003.
 5. Matricardi PM: Prevalence of atopy and asthma in Eastern versus Western Europe: why the difference? *Ann Allergy Asthma Immunol* 2001, 87:24–27.
 6. van Reijssen FC, Felijs A, Wauters EA, et al.: T-cell reactivity for a peanut-derived epitope in the skin of a young infant with atopic dermatitis. *J Allergy Clin Immunol* 1998, 101:207–209.
 7. Eigenmann PA, Sicherer SH, Borkowski TA, et al.: Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998, 101:E8.
 8. Kramer MS, Kakuma R: Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. *Cochrane Database Syst Rev* 2006, 3:CD000133.
 - 9.•• Greer FR, Sicherer SH, Burks AW, et al.: Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008, 121:183–191.
- This consensus statement recommends against delayed introduction of solid food in most cases.
10. Zutavern A, Brockow I, Schaaf B, et al.: Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. *Pediatrics* 2008, 121:e44–e52.
 11. Chatzi L, Torrent M, Romieu I, et al.: Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax* 2008, 63:507–513.
 12. Willers SM, Devereux G, Craig LC, et al.: Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. *Thorax* 2007, 62:773–779.
 - 13.• Garcia-Marcos L, Canflanca IM, Garrido JB, et al.: Relationship of asthma and rhinoconjunctivitis with obesity, exercise and Mediterranean diet in Spanish schoolchildren. *Thorax* 2007, 62:503–508.
- This cross-sectional study included more than 20,000 children and not only found a Mediterranean diet to be protective against atopic disease but also found fast food to increase children's risk of developing atopy.
14. Chatzi L, Apostolaki G, Bibakis I, et al.: Protective effect of fruits, vegetables and the Mediterranean diet on asthma and allergies among children in Crete. *Thorax* 2007, 62:677–683.
 15. Weitzman M, Gortmaker S, Walker DK, Sobol A: Maternal smoking and childhood asthma. *Pediatrics* 1990, 85:505–511.
 16. Young S, Le Souef PN, Geelhoed GC, et al.: The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991, 324:1168–1173.
 17. Martinez FD, Cline M, Burrows B: Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992, 89:21–26.
 18. Strachan DP, Cook DG: Health effects of passive smoking. 5. Parental smoking and allergic sensitisation in children. *Thorax* 1998, 53:117–123.
 - 19.•• Lannero E, Wickman M, van Hage M, et al.: Exposure to environmental tobacco smoke and sensitization in children. *Thorax* 2008, 63:172–176.
- This study found that exposure to tobacco smoke can increase a child's risk not only of developing asthma but also of developing atopic sensitization.
20. Korsgaard J: Mite asthma and residency. A case-control study on the impact of exposure to house-dust mites in dwellings. *Am Rev Respir Dis* 1983, 128:231–235.
 21. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ: Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990, 323:502–507.

22. Wahn U, Lau S, Bergmann R, et al.: Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997, 99:763–769.
 23. Lau S, Illi S, Sommerfeld C, et al.: Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. *Lancet* 2000, 356:1392–1397.
 24. Horak F Jr, Matthews S, Ihorst G, et al.: Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study—24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy* 2004, 34:1220–1225.
 25. Simpson A, Simpson B, Custovic A, et al.: Stringent environmental control in pregnancy and early life: the long-term effects on mite, cat and dog allergen. *Clin Exp Allergy* 2003, 33:1183–1189.
 26. Custovic A, Simpson BM, Simpson A, et al.: Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. *Lancet* 2001, 358:188–193.
 27. Arshad SH, Bateman B, Sadeghnejad A, et al.: Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007, 119:307–313.
- This landmark trial was the first to combine dust mite avoidance with avoidance of highly antigenic foods in high-risk children and successfully decrease atopic sensitization.
28. von Mutius E: Asthma and allergies in rural areas of Europe. *Proc Am Thorac Soc* 2007, 4:212–216.
 29. Strachan DP: Hay fever, hygiene, and household size. *BMJ* 1989, 299:1259–1260.
 30. Schram D, Doekes G, Boeve M, et al.: Bacterial and fungal components in house dust of farm children, Rudolf Steiner school children and reference children—the PARSIFAL Study. *Allergy* 2005, 60:611–618.
 31. Braun-Fahrlander C, Riedler J, Herz U, et al.: Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002, 347:869–877.
 32. van Strien RT, Engel R, Holst O, et al.: Microbial exposure of rural school children, as assessed by levels of N-acetyl-muramic acid in mattress dust, and its association with respiratory health. *J Allergy Clin Immunol* 2004, 113:860–867.
 33. Schram-Bijkerk D, Doekes G, Douwes J, et al.: Bacterial and fungal agents in house dust and wheeze in children: the PARSIFAL study. *Clin Exp Allergy* 2005, 35:1272–1278.
 34. Lehtinen P, Ruohola A, Vanto T, et al.: Prednisolone reduces recurrent wheezing after a first wheezing episode associated with rhinovirus infection or eczema. *J Allergy Clin Immunol* 2007, 119:570–575.
- This study provides evidence for treating first wheezing episodes with prednisolone to reduce the risk of persistent wheezing.
35. Allmers H: Frequent acetaminophen use and allergic diseases: is the association clear? *J Allergy Clin Immunol* 2005, 116:859–862.
 36. Micheli L, Cerretani D, Fiaschi AI, et al.: Effect of acetaminophen on glutathione levels in rat testis and lung. *Environ Health Perspect* 1994, 102(Suppl 9):63–64.
 37. Davey G, Berhane Y, Duncan P, et al.: Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in Butajira, Ethiopia. *J Allergy Clin Immunol* 2005, 116:863–868.
 38. Perzanowski MS, Ali DB, Garfinkel RS, et al.: Prenatal acetaminophen use is a risk for wheeze at age 5 years in a low income urban population with a high risk for asthma. *J Allergy Clin Immunol* 2008, 121:S231.
 39. Kozyrskyj AL, Ernst P, Becker AB: Increased risk of childhood asthma from antibiotic use in early life. *Chest* 2007, 131:1753–1759.
 40. Celedon JC, Litonjua AA, Ryan L, et al.: Lack of association between antibiotic use in the first year of life and asthma, allergic rhinitis, or eczema at age 5 years. *Am J Respir Crit Care Med* 2002, 166:72–75.
 41. Kukkonen K, Savilahti E, Haahtela T, et al.: Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2007, 119:192–198.
 42. Lee J, Seto D, Bielory L: Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. *J Allergy Clin Immunol* 2008, 121:116–121.